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(54) Title: IMMUNOMODULATORY, ANTI-INFLAMMATORY, AND ANTI-PROLIFERATIVE COMPOUNDS: 5,6-DIDEOXY, 5-AMINO DERIVATIVES OF IDOSE AND 6-DEOXY, 6-AMINO DERIVATIVES OF GLUCOSE

(57) Abstract

Compounds of this invention are 5,6-dideoxy, 5-amino derivatives of idose and 6-deoxy, 6-amino derivatives of glucose which exhibit immunomodulatory, anti-inflammatory, and anti-proliferative activity. Methods of preparation, pharmaceutical compositions containing the compounds and methods of treating inflammatory and/or autoimmune disorders employing the compounds are disclosed.

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IMMUNOMODULATORY, ANTI-INFLAMMATORY, AND ANTI-PROLIFERATIVE COMPOUNDS: 5,6-DIDEOXY, 5-AMINO DERIVATIVES OF IDOSE AND 6-DEDOXY, 6-AMINO DERIVATIVES OF GLUCOSE

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to deoxy, amino derivatives of idose and glucose which exhibit immunomodulatory, anti-inflammatory, and anti-proliferative activity. Compounds of the invention are useful for treating mammals with inflammatory and/or autoimmune disorders. This invention also relates to pharmaceutical compositions containing the disclosed compounds and to methods of treating inflammatory and/or autoimmune disorders employing the disclosed compounds.

Description of the Related Art

Derivatives of certain monosaccharides are known to have therapeutic value in the treatment of inflammatory and autoimmune disorders. Preparation of derivatives of these sugars can generally be accomplished by synthetic techniques which are known in the art.

To prepare derivatives of the monosaccharides, it is common to block or protect one or more of the hydroxyl groups with acetal blocking groups such as isopropylidene or cyclohexylidene groups and leave only one or two hydroxyl groups free to undergo further reaction. Various blocking groups and methods are described in U.S. Patent Nos. 2,715,121 and 4,056,322 and the disclosures of these patents are incorporated herein by reference. For example, to prepare a derivative of α,D-glucose which is blocked in its furanose ring structure, the 1,2- and 5,6-hydroxyl groups can be blocked using an isopropylidene blocking group and the 3-position left open to undergo further reaction. After the reaction to derivatize the 3-position is compl t , the blocking groups may be selectively remov d to allow f r further derivatization at other positions if desired.

Various derivatives of monosaccharides, as well as synthetic methods for their preparation, are described in U.S. Patent Nos. Re. 30,354, Re. 30,379, Re. 32,268, 4,056,322, 4,735,934, 4,738,953, 4,996,195, 5,010,058, and 5,298,494. The therapeutic activity of various monosaccharides and their derivatives is also disclosed in these documents. The disclosures of these documents are incorporated herein by reference.

Two well known derivatives of α,D-glucose having beneficial therapeutic properties are amiprilose, which is 1,2-O-Isopropylidene-3-O-3'-(N,N'-dimethylamino-n-propyl)-α,D-glucofuranose, and its hydrochloric acid salt, amiprilose HCl (THERAFECTIN®). These compounds are known to have anti-inflammatory activity and demonstrate utility in managing the signs and symptoms of rheumatoid arthritis. More generally, these compounds have activity as immunomodulators, and therefore have a therapeutic effect on autoimmune disorders such as, for example, rheumatoid arthritis and psoriasis.

Deoxy derivatives of 1,2-O-Isopropylidene-α, D-glucofuranose are described in U.S. Patent No. 5,010,058, the disclosure of which is incorporated herein by reference. That patent describes methods of preparing deoxy derivatives of 1,2-O-Isopropylidene-α,D-glucofuranose, and the use of such compounds in treating mammals with inflammatory and/or autoimmune disorders.

While some prior art monosaccharide derivatives have shown beneficial therapeutic activity, high doses of such compounds may often be needed to be effective and produce the desired results. Because therapy for inflammatory and autoimmune disorders is often chronic, there is a continuing need to develop potent, nontoxic compounds which can be orally administered to promote ease of treatment and patient compliance.

The present invention, therefore, is directed to new compounds and pharmaceutical compositions that exhibit greater potency than available compounds and compositions.

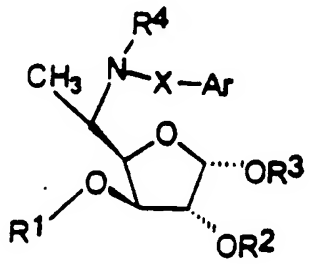
The present invention is also directed to a method of treating an animal or human suffering from an inflammatory and/or autoimmune disorder.

Other advantages of the invention are set forth in the description which follows, will be apparent from the description, or may be learned by practice of the invention.

SUMMARY OF THE INVENTION

To achieve the above objects, and in accordance with the purpose of the invention as embodied and broadly described here, there is provided:

A 5,6-dideoxy, 5-amino derivative of idose of the formula (I):



(I)

wherein

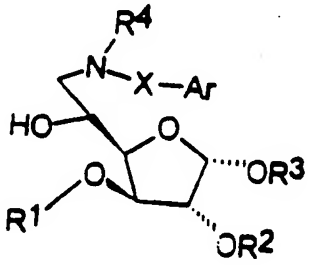
R^1 is a C_3 to C_{15} branched or unbranched alkyl group, or an alkyl-cycloalkyl group;

R^2 and R^3 together with the atoms carrying them form an acetal protecting group;

Ar is a substituted or unsubstituted, aromatic or heteroaromatic group selected from the group consisting of imidazolyl, furanyl, pyrrolyl, 1,3-benzodioxol-5-ylmethyl, pyridinyl, thienyl, naphthyl, and phenyl;

R^4 is hydrogen or a branched or unbranched lower alkyl group having 1 to 5 carbon atoms; and
X is a bond, or a branched or unbranched lower alkylene group having 1 to 5 carbon atoms, or together with R^4, and the nitrogen carrying them, forms a 5-, 6-, or 7-membered heterocycle fused to the aromatic or heteroaromatic group Ar;
or a physiologically acceptable salt thereof.

A 6-deoxy, 6-amino derivative of glucose of the formula (II):



(II)

wherein

R^1 is a C_3 to C_{15} branched or unbranched alkyl group, or an alkyl-cycloalkyl group;
R^2 and R^3 together with the atoms carrying them form an acetal protecting group;
Ar is a substituted or unsubstituted, aromatic or heteroaromatic group selected from the group consisting of imidazolyl, furanyl, pyrrolyl, 1,3-benzodioxol-5-ylmethyl, pyridinyl, thienyl, naphthyl, and phenyl;
R^4 is hydrogen or a branched or unbranched lower alkyl group having 1 to 5 carbon atoms; and
X is a bond, or a branched or unbranched lower alkylene group having 1 to 5 carbon atoms, or together with R^4, and the nitrogen carrying them,

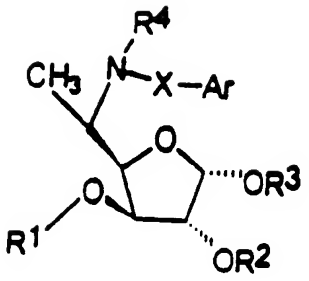
forms a 5-, 6-, or 7-membered heterocycle fused to said aromatic or heteroaromatic group Ar;
or a physiologically acceptable salt thereof.

The immunomodulatory, anti-proliferative, and/or anti-inflammatory compounds of formulae I and II exhibit beneficial therapeutic properties and are useful in the treatment of inflammatory and autoimmune disorders. Specifically, these compounds have demonstrated inhibitory effects on lymphocyte proliferation, immunomodulatory, and anti-inflammatory activity in art recognized *in vitro* and *ex vivo* screening tests. Compounds having this activity are useful, for example, in treating animals and humans with various chronic inflammatory and/or autoimmune conditions such as, but not limited to, rheumatoid arthritis, psoriasis, psoriatic arthritis, scleroderma, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, osteoarthritis, and asthma.

The present invention also provides pharmaceutical compositions containing the subject 5,6-dideoxy, 5-amino-derivatives of idose or 6-deoxy, 6-amino-derivatives of glucose, and methods for the treatment of inflammatory and/or autoimmune disorders employing those compounds. The pharmaceutical compositions comprise an effective amount of at least one of these compounds or a physiologically tolerated salt thereof, with a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the compounds of this invention are 5,6-dideoxy, 5-amino derivatives of idose and physiologically acceptable salts thereof. These compounds may be represented by formula (I):



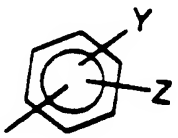
(I)

R^1 is selected from a C_3 to C_{15} branched or unbranched alkyl group, and an alkyl-cycloalkyl group. Preferably, R^1 is a C_4 to C_{12} unbranched alkyl or (C_1-C_3)-alkyl-(C_3-C_7)-cycloalkyl group. Most preferably, R^1 is pentyl, heptyl, decyl, dodecyl, cyclopropylmethyl, cyclohexylmethyl or cyclohexylpropyl.

R^2 and R^3 together with the atoms carrying them form an acetal protecting group. Preferably, the acetal protecting group is an isopropylidene group or a cyclohexylidene group. Most preferably, R^2 and R^3 form an isopropylidene group.

The group Ar is a substituted or unsubstituted, aromatic or heteroaromatic group selected from pyridinyl, furanyl, thienyl, pyrrolyl, 1,3-benzodioxol-5-ylmethyl, naphthyl, and phenyl.

Preferred groups for Ar are pyridinyl and substituted or unsubstituted phenyl of the formula:



Y and Z are each independently H, F, Cl, Br, OCH_3, CN, NO_2, CF_3, OCF_3 or NR'R'', wherein R' and R'', which may be the same or different, are a branched or non-branched alkyl group, preferably having 1 to 6 carbon atoms, which may be substituted or non-substituted. Particularly preferred are compounds where X and Ar together form a group selected from 2-pyridinyl, 4-pyridinyl, (2-

pyridinylmethyl), (2-pyridinylethyl), (2-furanylmethyl), 1,2,3,4-tetrahydroisoquinolinyl, (2-fluorophenyl)methyl, (4-pyridinylmethyl), (3-methoxyphenyl)methyl, 3-(N-imidazolyl) propyl, (4-chlorophenyl)methyl, (3-chlorophenyl)methyl, (2-chlorophenyl)methyl, (4-fluorophenyl)methyl, (3-fluorophenyl)methyl, (4-bromophenyl)methyl, (4-trifluoromethylphenyl)methyl, (4-trifluoromethoxyphenyl)methyl, (2,4-dichlorophenyl)methyl, (2,4-difluorophenyl)methyl, (2,3-dimethoxyphenyl)methyl, and (3,5-dimethoxyphenyl)methyl.

R^4 is a hydrogen or a branched or unbranched lower alkyl group having 1 to 5 carbon atoms. Preferably, R^4 is hydrogen, methyl, ethyl or propyl and most preferably hydrogen or methyl.

The divalent group X is a bond or is selected from a branched or unbranched lower alkylene group having 1 to 5 carbon atoms or together with R^4, and the nitrogen carrying them, forms a 5-, 6-, or 7-member heterocycle fused to the aromatic or heteroaromatic group Ar. Preferably, when X is an alkylene group, it is a C_1-C_4 alkylene group. Most preferably, X is a bond, i.e., a bond joining Ar and N, or a methylene, ethylene, propylidene, or 2'-propylidene group. When X together with R^4, and the nitrogen carrying them, form a 5-, 6- or 7-member heterocyclic fused to the aromatic or heteroaromatic group Ar, the preferred group is a hydrogenated isoquinoline group, preferably tetrahydroisoquinolinyl.

Preferred compounds of formula I include:

1,2-O-Isopropylidene-3-O-decyl-5,6-dideoxy-5-N-[(2-pyridinylmethyl)amino]-β,L-idofuranose, (Ia);

1,2-O-Isopropylidene-3-O-decyl-5,6-dideoxy-5-N-[(2-furanylmethyl)amino]-β,L-idofuranose, (Ib);

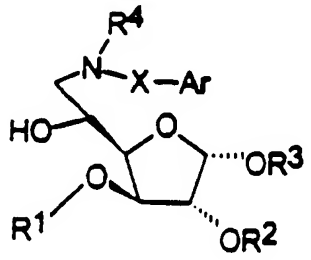
1,2-O-Isopropylidene-3-O-decyl-5,6-dideoxy-5-N-[[2-(2-pyridinyl)ethyl]amino]-β,L-idofuranose, (Ic);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-5,6-dideoxy-5-N-[(4-pyridinylmethyl)amino]-β,L-idofuranose, (Id) and

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-5,6-dideoxy-5-N-[(2-pyridinylmethyl)amino]-β,L-idofuranose, (Ie).

Particularly preferred are compounds Ia and Ib.

According to another embodiment, this invention includes compounds which are 6-deoxy, 6-amino derivatives of glucose or physiologically acceptable salts thereof. These derivatives may be represented by formula II:



(II)

The groups R^1, R^2, R^3 and R^4, Ar and X in formula II have the same meaning and preferred embodiments as described for formula I. Preferred compounds of formula II include:

1,2-O-Isopropylidene-3-O-decyl-6-deoxy-6-N-(1,2,3,4-tetrahydroisoquinolinyl)-α,D-glucofuranose, (IIa);

1,2-O-Isopropylidene-3-O-decyl-6-deoxy-6-N-[[(3,4-difluorophenyl)methyl]amino]-α,D-glucofuranose, (IIb);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(2-fluorophenyl)methyl]amino]-α,D-glucofuranose, (IIc);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose, (IId);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose hydrochloride, (IIe);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(4-pyridinylmethyl)amino]-α,D-glucofuranose, (IIf);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(3-methoxyphenyl)methyl]amino]-α,D-glucofuranose, (IIg);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[3-(N-imidazolyl)propyl]amino]-α,D-glucofuranose, (IIh);

1,2-O-Isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[2-(2-pyridinyl)ethyl]amino]-α,D-glucofuranose, (IIi);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[(phenylmethyl)amino]-α,D-glucofuranose, (IIj);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[(3-pyridinylmethyl)amino]-α,D-glucofuranose, (IIk);

1,2-O-Isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[4-(1-benzyl)piperidinyl]amino]-α,D-glucofuranose, (IIl);

1,2-O-Isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[(2-trifluoromethylphenyl)methyl]amino]-α,D-glucofuranose, (IIm);

1,2-O-Isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[(4-trifluoromethylphenyl)methyl]amino]-α,D-glucofuranose, (IIn);

1,2-O-Isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[(3-trifluoromethylphenyl)methyl]amino]-α,D-glucofuranose, (IIo);

1,2-O-Isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[2-(3-chlorophenyl)ethyl]amino]-α,D-glucofuranose, (IIp);

1,2-O-Isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[2-(4-chlorophenyl)ethyl]amino]-α,D-glucofuranose, (IIq);

1,2-O-Isopropylidene-3-O-dodecyl-6-N-[[2-(2-chlorophenyl)ethyl]amino]-α,D-glucofuranose, (IIr);

1,2-O-Isopropylidene-3-O-heptyl-6-N-[[(2-methoxyphenyl)methyl]amino]-α,D-glucofuranose, (IIs);

1,2-O-Isopropylidene-3-O-heptyl-6-N-[[(3-methoxyphenyl)methyl]amino]-α,D-glucofuranose, (IIt);

1,2-O-Isopropylidene-3-O-heptyl-6-N-[[(4-methoxyphenyl)methyl]amino]-α,D-glucofuranose, (IIu);

1,2-O-Isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]-α,D-glucofuranose, (IIv);

1,2-O-Isopropylidene-3-O-dodecyl-6-deoxy-6-N-[(2-thienymethyl)amino]-α,D-glucofuranose, (IIw);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(3-fluorophenyl)methyl]amino]-α,D-glucofuranose, (IIx);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[2-(4-methoxyphenyl)ethyl]amino]-α,D-glucofuranose, (IIy);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(3-chlorophenyl)methyl]amino]-α,D-glucofuranose, (IIz);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(4-chlorophenyl)methyl]amino]-α,D-glucofuranose, (IIaa);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]-α,D-glucofuranose, (IIbb);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N- [(phenylmethyl)amino]-α,D-glucofuranose, (IIcc);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[(3-phenylpropyl)amino]-α,D-glucofuranose, (IIdd);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(1-methyl-3- phenyl)propyl]amino]-α,D-glucofuranose, (IIee);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[2-(1-methyl- pyrrol-2-yl)ethyl]amino]-α,D-glucofuranose, (IIff);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4- fluorophenyl)methyl]amino]-α,D-glucofuranose, (IIgg);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(2- pyridinylmethyl)amino]-α,D-glucofuranose, (IIhh);

1,2-O-Isopropylidene-3-O-decyl-6-deoxy-6-N-[(1,3-benzodioxol-5-ylmethyl)amino]-α,D-glucofuranose, (IIii);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(2,4-dichlorophenyl)methyl]amino]-α,D-glucofuranose, (IIjj);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(2,3-dimethoxyphenyl)methyl]amino]-α,D-glucofuranose, (IIkk);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(3,5-dimethoxyphenyl)methyl]amino]-α,D-glucofuranose, (IIll);

1,2-O-Isopropylidene-3-O-decyl-6-deoxy-6-N-[[(3,4-dichlorophenyl)methyl]amino]-α,D-glucofuranose, (IImm);

1,2-O-Isopropylidene-3-O-decyl-6-deoxy-6-N-[[(2,6-difluorophenyl)methyl]amino]-α,D-glucofuranose, (IInn);

1,2-O-Isopropylidene-3-O-(3'-cyclohexylpropyl)-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose, (IIoo);

1,2-O-Isopropylidene-3-O-(3'-cyclohexylpropyl)-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]-α,D-glucofuranose, (IIpp);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]-α,D-glucofuranose, (IIqq);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(3-chlorophenyl)methyl]amino]-α,D-glucofuranose, (IIrr);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-(1,2,3,4-tetrahydroisoquinolinyl)-α,D-glucofuranose, (IIss);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(2-thienylmethyl)amino]-α,D-glucofuranose, (IItt);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(1-naphthylmethyl)amino]-α,D-glucofuranose, (IIuu);

1,2-O-Isopropylidene-3-O-pentyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose, (IIvv);

1,2-O-Isopropylidene-3-O-pentyl-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]-α,D-glucofuranose, (IIww);

1,2-O-Isopropylidene-3-O-pentyl-6-deoxy-6-N-[[(3-chlorophenyl)methyl]amino]-α,D-glucofuranose, (IIxx);

1,2-O-Isopropylidene-3-O-cyclopropylmethyl-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]-α,D-glucofuranose, (IIyy);

1,2-O-Isopropylidene-3-O-cyclopropylmethyl-6-deoxy-6-N-[[(3-chlorophenyl)methyl]amino]-α,D-glucofuranose, (IIzz);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-chlorophenyl)methyl]amino]-α,D-glucofuranose, (IIaaa);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-trifluoromethylphenyl)methyl]amino]-α,D-glucofuranose, (IIbbb);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(3-fluorophenyl)methyl]amino]-α,D-glucofuranose, (IIccc);

1,2-O-Isopropylidene-3-O-pentyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]-α,D-glucofuranose, (IIddd);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]-α,D-glucofuranose, (IIeee);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]-α,D-glucofuranose, (IIfff);

1,2-O-Isopropylidene-3-O-cyclopropylmethyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]-α,D-glucofuranose, (IIggg);

1,2-O-Isopropylidene-3-O-(3'-cyclohexylpropyl)-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]-α,D-glucofuranose, (IIhhh);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(2,4-difluorophenyl)methyl]amino]-α,D-glucofuranose, (IIiii);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-trifluoromethoxyphenyl)methyl]amino]-α,D-glucofuranose, (IIjjj);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-(4-pyridinylamino)-α,D-glucofuranose, (IIkkk);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[(2-chlorophenyl)amino]-α,D-glucofuranose, (IIlll);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(3,4-difluorophenyl)methyl]amino]-α,D-glucofuranose, (IImmm);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-bromophenyl)methyl]amino]-α,D-glucofuranose, (IInnn);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(4-pyridinylmethyl)amino]-α,D-glucofuranose hydrochloride, (IIooo);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(3-methoxyphenyl)methyl]amino]-α,D-glucofuranose hydrochloride, (IIppp);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]-α,D-glucofuranose hydrochloride, (IIqqq);

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(3-chlorophenyl)methyl]amino]-α,D-glucofuranose hydrochloride, (IIrrr);

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]-α,D-glucofuranose hydrochloride, (IIsss); and

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose hydrochloride, (IIttt).

The following compounds are particularly preferred IIa, IIc, IId, IIe, IIf, IIg, IIh, IIz, IIbb, IIgg, IIhh, IIii, IIjj, IIkk, IIll, IIhhh, IIfff, IIggg, IIlll, IIooo, IIppp, IIqqq, IIrrr, IIsss and IIttt. Most preferred are compounds IIe, IIppp, IIqqq, IIrrr, IIsss, and IIttt.

The immunomodulatory, anti-proliferative and/or anti-inflammatory compounds of the present invention also include physiologically acceptable salts of the compounds of formulae (I) and (II). Preferred physiologically acceptable salts are acid-addition salts. Common physiologically acceptable acid-addition salts include but are not limited to, hydrochloric acid salts, oxalate salts and tartrate salts.

The compounds of the invention may be prepared according to a general synthetic procedure. The examples below demonstrate the general synthetic procedure, as well as the specific preparation, for compounds according to this invention. The examples are illustrative, and are not intended to limit, in any manner, the claimed invention.

The general synthetic procedure can be describ d as follows. First, a suitably protected hexofuranose having

a free hydroxyl group is alkylated at that hydroxyl group with a base and an appropriate alkyl halide. Selective removal of a protecting group provides an intermediate which can be preferentially tosylated. If tosylated at the 6-position, the resulting tosylate is then displaced upon treatment with an appropriate primary or secondary amine to give the deoxy, 6-amino compounds of formula (II) directly. Alternatively, compounds having a tosylate group at the 6-position can be reduced with a suitable reducing agent to yield an intermediate which, upon a second tosylation at the 5-position and subsequent reaction with an appropriate primary or secondary amine gives compounds according to formula (I).

Pharmacologic Activity

Compounds of the present invention have demonstrated immunomodulatory, anti-inflammatory, and anti-proliferative effects in biological assays. Standard *in vitro* and *ex vivo* immunologic assays were performed on compounds of the present invention in order to assess immunomodulatory, anti-inflammatory, and anti-proliferative activity. These included the mouse Arachidonic Acid Ear assay, the *ex vivo* Macrophage Phagocytosis assay, the *in vitro* and *ex vivo* Mixed Lymphocyte Response (MLR), and the *in vitro* mouse Mitogen-Induced T Lymphocyte Proliferation assay.

The MLR functions as a test of immunomodulatory effects of the compounds whereby inhibitory effects on T lymphocyte activation and antigen presentation are determined. Further immunomodulatory effects were analyzed in an *ex vivo* Macrophage Phagocytosis assay.

Anti-proliferative effects were demonstrated by measuring the inhibitory effects of compounds of the present invention on the cellular proliferation of Concanavalin A stimulated murine splenocytes.

Anti-inflammatory effects w re determined in a mouse Arachadonic Acid Ear assay.

Inflammation and mechanisms involved in the pathogenesis of autoimmune diseases involve cellular activation and proliferation as well as abnormal immune system activation. Therefore, the assays employed here are appropriate and accepted screens for novel compounds in the treatment of inflammatory and/or autoimmune disorders.

The compounds of the present invention have demonstrated immunomodulatory, anti-inflammatory, and anti-proliferative activities. Concentrations tested in *in vitro* assays ranged from 0.00001 to 10 μg/mL and 5 to 25 mg/kg in *ex vivo* assays. Compounds of the present invention uniformly demonstrated potent *in vitro* and *ex vivo* immunomodulatory and anti-proliferative effects. These results indicate that compounds of the present invention are highly active agents with potent *in vitro* and *ex vivo* activities.

The 5,6-dideoxy, 5-amino- derivatives of idose and 6-deoxy, 6-amino-derivatives of glucose of the invention are useful for treating animals and mammals with various chronic inflammatory and/or autoimmune conditions such as, but not limited to, rheumatoid arthritis, psoriasis, psoriatic arthritis, scleroderma, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, osteoarthritis, and asthma. Due to their valuable pharmacological properties, the compounds of the present invention or their physiologically acceptable salts, are particularly suitable for use as active compounds in pharmaceutical compositions for the treatment of, for example, rheumatic inflammatory disorders.

The compounds described above can either be administered alone in the form of microcapsules, in mixtures with one another, or in combination with acceptable pharmaceutical carriers. The invention, thus, also relates to pharmaceutical compositions which comprise an effective amount of at least one compound of the invention with or without a pharmaceutically or

physiologically acceptable carrier. If appropriate, the compound may be administered in the form of a physiologically acceptable salt, for example, an acid-addition salt.

The present invention also encompasses a method of treating animals or humans suffering from one or more of the inflammatory and/or autoimmune disorders discussed above. This method comprises administering to the animal or person an effective amount of at least one of the compounds of the invention, or a physiologically acceptable salt thereof, with or without a pharmaceutically acceptable carrier. The compounds according to the invention can be administered orally, topically, rectally, anterally, internally, by boluses or, if desired, parenterally. Oral administration is preferred.

Suitable solid or liquid formulations are, for example, granules, powders, coated tablets, microcapsules, suppositories, syrups, elixirs, suspensions, emulsions, drops or injectable solutions. Also, the compounds of the invention may be employed in preparations having a protracted release of the active compound. Commonly used additives in protracted release preparations are excipients, disintegrates, binders, coating agents, swelling agents, glidants, or lubricants, flavors, sweeteners or solubilizers. More specifically, frequently used additives are, for example, magnesium stearate, magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, lactalbumin, gelatin, starch, cellulose and its derivatives, animal and vegetable oils, polyethylene glycols and solvents. Common solvents include sterile water and monohydric or polyhydric alcohols such as glycerol.

The pharmaceutical compositions are preferably produced and administered in dosage units, each unit containing as an active component an effective dose of at least one compound of the present invention and/or at

least one of its physiologically acceptable salts. In the case of mammals, the effective dose to treat autoimmune and/or anti-inflammatory disorders can range from about 1 to 100 mg/kg of body weight per day.

EXAMPLES

The following examples demonstrate the preparation of compounds according to this invention. The examples are illustrative, and are not intended to limit, in any manner, the claimed invention.

Example 1: Preparation of 1,2-O-Isopropylidene-3-O-decyl-5,6- dideoxy-5-N-[(2-pyridinylmethyl)amino]-β,L-idofuranose (Ia).

Preparation of 1,2:5,6-Di-O-Isopropylidene-3-O-decyl-α,D-glucofuranose.

1,2:5,6-Di-O-Isopropylidene-α,D-glucofuranose (101g, 0.39mol) was combined with dried, crushed sodium hydroxide (46.17g, 1.1543mol) and decylbromide (105.4g, 0.4768mol) in a round bottom flask. The reaction was stirred at 127-130°C, and monitored by TLC (70% ether in hexane). After two hours the reaction was cooled. The mixture was extracted with ether, filtered, and concentrated. The compound was chromatographed on silica gel, eluting with 30% ether in hexane. The title compound was obtained in 96% yield (149g).

Preparation of 1,2-O-Isopropylidene-3-O-decyl-α,D-glucofuranose.

1,2:5,6-Di-O-Isopropylidene-3-O-decyl-α,D-glucofuranose (92g) was dissolved in THF (95mL) in a round bottom flask and cooled to 0-5°C, with stirring. Perchloric acid (30% vol.) was added drop-wise to the solution at a rate of 1 drop/sec. The reaction was monitored by TLC (70% ether in hexane). After 25 minutes the reaction was quenched by drop-wise addition of a saturated potassium carbonate solution. The reaction

mixture was dilut d with THF. When the reaction reached a pH of 7-8, the reaction was filtered, and THF was evaporated. The resulting mixture was extracted with ether and the water removed by separatory funnel and magnesium sulfate. The organic layer was filtered and concentrated. The compound was chromatographed on silica gel, eluting with 30%-40% ether in hexane. The desired product was obtained in 68% yield (56.4g).

Preparation of 1,2-O-Isopropylidene-3-O-decyl-6-O-tosyl-α,D-glucofuranose.

1,2-O-Isopropylidene-3-O-decyl-α,D-glucofuranose (21.7g, 0.0603mol) was dissolved in pyridine in a round bottom flask equipped with a drying tube and cooled to 0-5°C with stirring. Tosyl chloride (11.55g, 0.0606mol) was dissolved in pyridine (50 mL total) and added drop-wise to the solution at a rate of 1 drop/sec. The reaction was monitored by TLC (50% ether in hexane). After 2 hours the reaction was poured into ice water (50 mL) and extracted with ether. The organic layer was then washed three times each with water, saturated sodium bicarbonate, and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The compound was chromatographed on silica gel, eluting with 20% ether in hexane to ether. The desired tosylate was obtained in 87% yield (24.1g). Some impurity remained, but the compound was usable in further synthesis.

Preparation of 1,2-O-Isopropylidene-3-O-decyl-6-deoxy-α,D-glucofuranose.

Lithium Aluminum Hyride (LAH) (3.62g, 0.0953mol) was placed in a round bottom flask equipped with a drying tube and cooled to 0-5°C with stirring. Tetrahydrofuran (20mL) was added drop-wise to the LAH at a rate of 1 drop/sec. (10 minute addition time). 1,2-O-Isopropylidene-3-O-decyl-6-O-tosyl-α,D-glucofuranose (24.5g, 0.0477mol) was dissolved in THF (35mL, anhydrous) and added drop-wise to

the slurry at a rate of 1drop/sec. (1.5 hours addition time). The reaction was monitored by TLC (30% ether in hexane). After 86 minutes, the reaction was quenched by drop-wise addition of water (10mL), then drop-wise addition of sodium hydroxide solution (10mL, 15% wt.) The reaction was diluted with THF and filtered. Tetrahydrofuran was removed, and the residue was dissolved in ether. Any residual water was removed by separatory funnel, then magnesium sulfate. The organic layer was filtered and concentrated. The compound was chromatographed on silica gel, eluting with 10% ether in hexane to ether. The title compound was obtained in 80% yield (13.2g).

Preparation of 1,2-O-Isopropylidene-3-O-decyl-5-O-tosyl-6-deoxy-α,D-glucofuranose.

1,2-O-Isopropylidene-3-O-decyl-6-deoxy-α,D-glucofuranose (13g, 0.0378mol) was combined with tosyl chloride (14.28g, 0.0750mol) and pyridine (20mL) in a round bottom flask equipped with a drying tube. The reaction was stirred and monitored by TLC (80% ether in hexane). After 27 hours, the reaction was poured into ice water and extracted with ether. The organic layer was then washed three times each with water, saturated sodium bicarbonate, and brine. The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The compound was chromatographed on silica gel and eluted with 10% ether in hexane. The title compound was obtained in 61% yield (11.5g).

Preparation of 1,2-O-Isopropylidene-3-O-decyl-5,6-dideoxy-5-N-[(2-pyridinylmethyl)amino]-β,L-idofuranose (Ia).

1,2-O-Isopropylidene-3-O-decyl-5-O-tosyl-6-deoxy-α,D-glucofuranose (2.0g) was combined with 2-(methylamino)-pyridine (8mL) in a round bottom flask and stirred at 100°C. The reaction was monitored by TLC (50%

ether in hexane). After 4 hours and 10 minutes, the reaction was cooled. The reaction was extracted with ether and washed one time each with water, saturated sodium bicarbonate, and brine. The organic layer dried over magnesium sulfate, filtered, and concentrated. The compound was chromatographed on silica gel, eluting with ether. The desired product, compound Ia, was obtained in 68% yield (1.18g).

Example 2: Preparation of 1,2-O-Isopropylidene-3-O-decyl-6-deoxy-6-N-(1,2,3,4-tetrahydroisoquinolinyl)-α,D-glucofuranose (IIa).

1,2-O-Isopropylidene-3-O-decyl-6-O-tosyl-α,D-glucofuranose (2.3g) was combined with tetrahydroisoquinoline (6mL) in a round bottom flask, and stirred at 73-75°C. The reaction was monitored by TLC (50% ether in hexane). After 1.5 hours, the reaction was cooled. The reaction was extracted with ether and washed three times each with water, saturated sodium bicarbonate, and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The compound was chromatographed on silica gel, eluting with ether. Compound IIa was obtained in 61% yield (1.3g).

Example 3: Preparation of 1,2-O-Isopropylidene-3-O-decyl-6-deoxy-6-N-{[(3,4-difluorophenyl)methyl]amino}-α,D-glucofuranose (IIb).

1,2-O-Isopropylidene-3-O-decyl-6-deoxy-6-O-tosyl-α,D-glucofuranose (2.0g) was combined with 3,4-(difluoro)-benzylamine (5g) in a round bottom flask and stirred at 69-70°C. The reaction was monitored by TLC (50% ether in hexane). After 6 hours the reaction was cooled. Water was added to the reaction and the mixture extracted with ether. The organic layer was then washed three times each with water, saturated sodium bicarbonate, and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The compound was chromatographed on

silica gel, eluting with 50% ether in hexane. Compound IIb was obtained in 64% yield (1.2g).

Example 4: Preparation of 1,2-O-Isopropylidene-3-O-heptyl-6- deoxy-6-N-{[2-fluorophenyl)methyl]amino}-α,D-glucofuranose (IIc).

Preparation of 1,2:5,6-Di-O-Isopropylidene-3-O-heptyl-α,D-glucofuranose.

1.2:5,6-Di-O-Isopropylidene-α,D-glucofuranose (75.3g, 0.290mol) was combined with dried, crushed sodium hydroxide, (34.3g, 0.86mol), and heptylbromide, (62.6g, 0.345mol), in a round bottom flask. The reaction was heated with stirring and monitored by TLC (50% ether in hexane). After 6 hours at 100-130°C, and 16 hours at ambient temperature, the reaction was extracted with ether and filtered. The compound was chromatographed on silica gel, eluting with 10% ether in hexane. The title compound was obtained in 83% yield (86g).

Preparation of 1,2-O-Isopropylidene-3-O-heptyl-α,D-glucofuranose.

1,2;5,6-Di-O-isopropylidine-3-O-heptyl-α,D-glucofuranose (86g) was dissolved in tetrahydofuran (86mL) and cooled to 0-5°C with stirring. Perchloric acid (86mL, 30% vol.) was then added drop-wise at a rate of 1 drop/sec (23 minute addition time). Reaction was monitored by TLC (50% ether in hexane). After 10 minutes at 0-5°C and 16.5 hours at -20°C, the reaction was neutralized to pH 7-8 by drop-wise addition of saturated potassium carbonate solution. The reaction was filtered, and the tetrahydrofuran evaporated. The residue was dissolved in ether and any water present was removed by separatory funnel and magnesium sulfate. The organic layer was filtered and concentrated. The compound was chromatographed on silica gel, eluting with 20% ether in

hexane to ether. The desired compound was obtained in 69% yield (52.7g).

Preparation of 1,2-O-Isopropylidene-3-O-heptyl-6-O-tosyl-α,D-glucofuranose.

1,2-O-Isopropylidene-3-O-heptyl-α,D-glucofuranose (25.4g, 0.0799mol) was dissolved in pyridine (50mL) and stirred in a round bottom flask equipped with a drying tube at 0-5°C. Tosyl chloride (13.32g, 0.0699mol) was dissolved in pyridine (20mL) and added drop-wise to the reaction at a rate of 1 drop/sec. The reaction was monitored by TLC (50% ether in hexane). After 2 hours at 0-5°C and 15 hours at -20°C, and 5 hours at 0-5°C, the reaction was poured into ice water and extracted with ether. The organic layer was washed three times each with water, saturated sodium bicarbonate, and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The compound was chromatographed on silica gel, eluting with 10% ether to 40% ether in hexane. The desired tosylate was obtained in 87% yield (25.6g).

Preparation of 1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(2-fluoropheny)methyl]amino]-α,D-glucofuranose (IIc).

1,2-O-Isopropylidene-3-O-heptyl-6-O-tosyl-α,D-glucofuranose (3.4g) was combined with 2-fluorobenzylamine (9mL) in a round bottom flask. The reaction was stirred at 75°C and monitored by TLC (70% ether in hexane). After 5 hours the reaction was cooled. The reaction was extracted with ether and washed three times each with water, saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The compound was chromatographed on silica gel, eluting with 50% ether in hexane. Compound IIc was obtained in 48% yield (1.47g).

Example 5: Preparation of 1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose (IId).

1,2-O-Isopropylidene-3-O-heptyl-6-O-tosyl-α,D-glucofuranose (1.5g) was combined was 2-(aminomethyl)-pyridine (3mL) in a round bottom flask with stirring. The reaction was heated to 75-80°C and monitored by TLC (ether/ammonium hydroxide). After 2 hours, the reaction was dried under high vacuum to remove excess amine. The residue was dissolved in ether and washed once each with water, saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The compound was chromatographed on silica gel, eluting with ether to 5% MeOH in ether. Compound IId was obtained in 69% yield (0.9g).

Example 6: Preparation of 1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose hydrochloride salt (IIe).

1,2-O-Isopropylidene-3-O-heptyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose (4g) was dissolved in acetone (75mL). Hydrochloric acid (3N) was added drop-wise until solution became acidic. Ether (100mL) was added and the solution was cooled. The resulting crystals were filtered and washed with cooled ether. Compound IIe was obtained in 53% yield (2.3g).

Example 7: Preparation of 1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(4-pyridinylmethyl)amino]-α,D- glucofuranose (IIf).

Preparation of 1,2:5,6-Di-O-isopropylidene-3-O-cyclohexylmethyl-α,D-glucofuranose.

1,2:5,6-Di-O-isopropylidene-α,D-glucofuranose (5.05g, 0.0194mol) was combined with crushed, dried sodium hydroxide (2.8g, 0.0700mol) and cyclohexylmethylbromide (4.09g, 0.0231mol) in a round bottom flask. The reaction

was stirred at 140°C for 3.5 hours, left at -20°C for 15 hours, and stirred at 140°C for one hour. The reaction was monitored by TLC (70% ether in hexane). The reaction was cooled, extracted with ether, and filtered. The compound was chromatographed on silica gel, eluting with 10% ether in hexane. The desired product was obtained in 80% yield (3.4g). Some cyclohexylmethylbromide remained but the compound was usable in further synthesis.

Preparation of 1,2-O-Isopropylidene-3-O-cyclohexylmethyl-α,D-glucofuranose.

1,2:5,6-Di-O-isopropylidene-3-O-cyclohexylmethyl-α,D-glucofuranose (43g) was dissolved in tetrahydofuran (45mL) and cooled to 0-5°C with stirring. Perchloric acid (45mL, 30%vol) was added drop-wise to the solution at a rate of 1 drop/second (16 minute addition time). Reaction was monitored by TLC (ether). After 35 minutes, the reaction was quenched by drop-wise addition of potassium carbonate (saturated solution). The reaction was diluted with tetrahydrofuran. When the pH of the reaction reached 7-8, the mixture was filtered and the tetrahydrofuran was evaporated. The residue was dissolved in ether and water removed by separatory funnel and magnesium sulfate. The organic layer was filtered and concentrated. The compound was chromatographed on silica gel, eluting with 50% ether/hexane. The desired product was obtained in 55% yield (21g).

Preparation of 1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-O-tosyl-α,D-glucofuranose.

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-α,D-glucofuranose (21.0g, 66.4mmol) was dissolved in pyridine (30mL) in a round bottom flask equipped with a drying tube, and cooled to 0-5°C with stirring. Tosyl chloride (12.7g, 0.0664mol) was dissolved in pyridine (20mL) and added drop-wise to the reaction at a rate of 1 drop/sec.(30 minute addition time). The reaction was

monitored by TLC (70% ether in hexane). After 3 hours the reaction was poured into ice water and extracted with ether. The organic layer was washed three times each with water, saturated sodium bicarbonate, and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The compound was chromatographed on silica gel, eluting with 30% ether in hexane. The title compound was obtained in 67% yield (20.8g).

Preparation of 1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(4-pyridinylmethyl)amino]-α,D-glucofuranose (IIf).

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-O-tosyl-α,D-glucofuranose (2.3g) was combined with 4-(pyridinylmethyl)amine (8mL) in a round bottom flask. The reaction was stirred at 75°C and monitored by TLC (70% ether in hexane). After 3 hours the reaction was cooled and extracted with ether. The mixture was washed one time each with water, saturated sodium bicarbonate, and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The compound was chromatographed on silica gel, eluting with ether to 5% MeOH in ether. Compound IIf was obtained in 55% yield (1.1g).

Example 8: Preparation of 1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-{[3 methoxyphenyl)methyl] amino}-α,D-glucofuranose (IIg).

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-O-tosyl-α,D-glucofuranose (1.9g) was combined with 3-methoxybenzylamine (7mL) in a round bottom flask. The reaction was stirred at 75°C and monitored by TLC (ether/ammonium hydroxide). After 1.5 hours, the reaction was cooled and extracted with ether. The mixture was washed three times each with water, saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The

compound was chromatographed on silica gel, eluting with ether. Compound IIg was obtained in 34% yield (0.6g).

Example 9: Preparation of 1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-{[3-(N-imidazolyl)propyl] amino}-α,D-glucofuranose (IIh).

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-O-tosyl-α,D-glucofuranose (2.3g) was combined with N-(3-aminopropyl) imidazole (7mL) in a round bottom flask. The reaction was stirred at 75°C and monitored by TLC (50% ether in hexane). After 1 hour 43 minutes, the reaction was cooled. The crude reaction mixture was chromatographed on silica gel, eluting with ether to 5% MeOH in ether. Compound IIh was obtained in 7% yield (0.15g).

Example 10: Preparation of 1,2-O-Isopropylidene-3-O-n-heptyl-6-deoxy-6-N-(4-pyridinylamino)-α,D-glucofuranose (IIkkk)

1,2-Isopropylidene-3-O-n-heptyl-6-O-tosyl-α,D-glucofuranose (6.65g) was dissolved in p-dioxane (90mL) and to this was added 4-aminopyridine (5.09g). The reaction mixture was heated to 110°C for five hours then cooled to room temperature, concentrated under high vacuum and the residue obtained extracted with diethyl ether (4 x 50 ml). The combined ether extracts were washed with saturated sodium bicarbonate, dried ($MgSO_4$), filtered and concentrated. The crude reaction mixture was chromatographed on silica gel (90:10:0.1 chloroform/methanol/triethylamine) to give 1,2-O-Isopropylidene-3-O-n-heptyl-6-deoxy-6-N-(4-pyridinylamino)-α,D-glucofuranose (0.9g).

Example 11: Preparation of 1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(1-naphthylmethyl)amino-α,D-goucofuranose (IIuu).

1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-O-tosyl-α,D-glucofuranose (2.0g) was combined with 1-aminomethyl naphthylene (8mL) in a round bottom flask. The reaction mixture was heated, with stirring, at 70°C for 5 hours, cooled and chromatographed on silica gel (1:1 diethyl ether/hexane) to give 1,2-O-Isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(1-naphthylmethyl)amino-α,D-glucofuranose (1.32g).

Example 12: Mouse Arachidonic Acid Ear Assay.

To assess potential anti-inflammatory activity of compound IIe, a standard Mouse Arachidonic Acid Ear assay was performed. This assay tests the ability of a specific compound to antagonize an inflammatory response.

Specific Method: Compound IIe was applied topically to one ear of 3 Balb/CByJ mice at a concentration of 2 mg/10 μl. After 30 minutes, arachidonic acid was applied to both ears of each mouse. One half hour later, the mice were sacrificed and an 8 mm diameter section of each ear was weighed. The weights of the compound treated and untreated ears were compared as a measure of the anti-inflammatory properties of the compound. Results are expressed using a simple qualitative scoring system in which 0 = inactive, 1+ = slightly active, 2+ = moderately active and 3+ = highly active.

Results: The (highly active) anti-inflammatory effects of compound IIe were scored as 3+ based on the results of this assay.

Example 13: *Ex Vivo* Mixed Lymphocyte Response (MLR) Assay.

The potential immunomodulatory effects of compound IIe were studied in an *ex vivo* Mixed Lymphocyte Response (MLR) assay system. This assay tests the ability of a specific compound to regulate a cell mediated immune response involving lymphocyte cell activation and proliferation.

Specific Method: Balb/cJ mice were dosed orally for 7 days with 5, 10 or 25 mg/kg of compound IIe, with water only as the vehicle control or with 50 mg/kg of cyclophosphamide as the positive control. Dose groups consisted of 10 mice per group. At the end of the dosing period, mice were euthanized by cervical dislocation and their spleens were removed. Single cell suspensions of each spleen were prepared in culture medium (DMEM supplemented with 10% calf serum, 2 Mm glutamine, 500 units penicillin/streptomycin, and 4 x 10^{-5} M 2-mercapto-ethanol, sodium pyruvate, non-essential amino acids, essential amino acids, nucleic acids, and MEM vitamins) using a Teflon pestle. The cells were centrifuged at 1500 RPM and the pellets resuspended in ACT (0.15 M Tris, 0.14 M Ammonium Chloride, pH 7.2) in order to lyse the red blood cells. After a five minute incubation in a 37°C waterbath, the cells were washed and resuspended in culture medium.

The splenic lymphocytes were counted using an electronic Coulter Counter. Spleen cells from C57BL/6 mice were used as stimulator cells and were prepared in the same way. The stimulator cells were then treated with 100 μg/mL of mitomycin for 20 minutes at 37°C, then washed five times in culture medium. The proliferative response was measured by culturing x 10^5 responder spleen cells with 5 x 10^5 stimulator cells in 96- well microliter plates.

Syngeneic control cultures using mitomycin C treated spleen cells from normal BALB/c mice as the stimulator cells were run also. All cultures were run in triplicate. After incubation for 5 days at 37°C with 5% CO_2, the amount of cell proliferation was measured by adding 20 μl of MTT (3-[4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) (10 mg/mL in PBS) to each well. Plates were incubated for 4 hours at 37°C, after which 180 μl of supernatant were removed and 180 μl of 10% SDS in PBS were added. After an overnight incubation, the optical density

(OD) of each well was read on a Molecular Devices microplate reader at 570-650 nm.

The result for each mouse was determined by calculating the difference between the allogeneic cultures and the syngeneic cultures for each spleen cell population. The mean of the test article group was determined and compared to the mean of the control group.

Statistical analyses were made in Systat (version 4.0, Systat, Inc.). The Tukey multiple comparisons test was used to make pairwise comparisons between groups to detect statistically significant differences.

Results: The results of this study are presented in Table 1. Statistically significant inhibition of mixed lymphocyte responsiveness in treated mice was achieved at all doses of compound IIe.

TABLE 1
Effect of Compound IIe on a Mixed Lymphocyte Response (MLR) Assay in Mice

Group	Treatment	Dose (mg/kg)	Difference (mean ± SD)	% Change[1]	P Value[2]
1	Vehicle	-	1.057 ± 0.554	-	-
2	Compound IIe	5	-0.022 ± 0.935	-102	0.009*
3	Compound IIe	10	-0.135 ± 0.489	-113	0.004*
4	Compound IIe	25	0.108 ± 0.620	-90	0.028*
5	Cyclophosphamide	50	-0.665 ± 0.735	-163	<0.001*

[1]% change from the vehicle control
[2]Comparison to the vehicle control
*Statistically significant

Example 14: *Ex Vivo* Macrophage Phagocytosis Assay.

The potential immunomodulatory effects of compound IIe were studied in an *ex vivo* Macrophage Phagocytosis Assay system. Macrophage phagocytic activity is involved in antigen presentation and accessory cell function of macrophages, which are functions critical to cell mediated immunity.

Specific Method: Balb/cByJ mice were dosed orally for 7 days with 5, 10 or 25 mg/kg of compound IIe or with

water only as the vehicle control. Dose groups consisted of 10 mice per group. At the end of the dosing p riod, mice were euthanized by decapitation. The peritoneal macrophages were collected by injecting 5 mL of culture medium (RPMI-1640 with Hepes, supplemented with 10% fetal calf serum (FCS), 2 mM glutamine, and 500 units penicillin/streptomycin) into the peritoneal cavity of each mouse and collecting the wash.

The cells were centrifuged at 1500 rpm for 5 minutes and resuspended in 2 mL of culture medium. 12 μL of latex particles were added to each tube. Tubes were rotated overnight at 37°C. After incubation, the cells were underlaid with 2 mL of fetal calf serum and centrifuged at 1500 rpm for 10 minutes to form pellets. The pellets were resuspended in medium and again underlaid with serum and spun. The pellets were resuspended in 0.5 mL of medium, at least 200 viable cells were counted and the number of cells containing latex beads (phagocytic cells) was determined. The percent of phagocytic cells was determined.

The means for each group were determined. The percent phagocytic cells obtained from the test article treated group was compared to that obtained from the negative control treated group and the percent of control was calculated.

Statistical analyses were made in Systat (version 4.0, Systat, Inc.). The Tukey multiple comparisons test was used to make pairwise comparisons between groups to detect statistically significant differences.

Results: The results of this study are presented in Table 2. Increased phagocytic activity of macrophages from compound IIe treated mice was observed of all dose levels, with statistically significant increases observed in cultures from the 10 mg/kg dose group.

TABLE 2

Effect of Compound IIe on Macrophage Phagocytosis in Mice

Group	Treatment	Dose (mg/kg)	% Phagocytic cells (mean ± SD)	% Change[1]	P Value[2]
1	Vehicle	-	9.990 ± 2.976	-	-
2	Compound IIe	5	15.489 ± 5.590	55	0.136
3	Compound IIe	10	19.220 ± 7.533	92	0.003*
4	Compound IIe	25	13.740 ± 4.350	38	0.414

[1]% change from the vehicle control
[2]Comparison to the vehicle control
*Statistically significant

Example 15: *In Vitro* Cytotoxicity Screening.

Compounds of the present invention were screened in *in vitro* cytotoxicity screens to determine appropriate non-toxic levels for testing in activity screens.

Specific Method: A mouse macrophage cell line (P388D1) was used at mid-log phase growth to evaluate *in vitro* cytotoxicity. Varying dilutions of compound were prepared from stock solutions consisting of compound dissolved in DMSO at 100 mg/mL. Compound dilutions were added to 2 x 10^5 cells/well in 96 well microtitre plates. After 24 hours of incubation at 37°C and 5% CO_2, the viability of cells in each well was determined by trypan blue exclusion analysis. The effects of each compound on cellular viability were determined using the following formula:

% viable unknown/% of viable control = % viability.

Results: A compound was considered cytotoxic if less than 70% viability was observed. The following compounds were found to be cytotoxic at an *in vitro* concentration of 1-10 μg/mL and were not subjected to a comprehensive testing regimen: IIi, IIj, IIt, IIv, IIw, IIy, IIaa, IIcc, IIdd, IIee.

Example 16: *In Vitro* Concanavalin A (Con A) Stimulated T Lymphocyte Proliferation Assay.

Compounds of the invention were tested for inhibitory effects on T lymphocyte activation and proliferation in an in *vitro* Concanavalin A (Con A) Stimulated T Lymphocyte Proliferation Assay.

Specific Method: Balb/cByJ mice were euthanized by cervical dislocation and their spleens were removed aseptically. Single cell splenic lymphocyte suspensions were prepared in buffered Earles Balanced Salt Solution (EBSS). Erythrocytes were removed by water lysis and spleen cells were resuspended in complete media (CM) consisting of RPMI 1640 media supplemented with 10% fetal calf serum, 1 mM Hepes buffer, 1 mM L-glutamine, 100 U Penicillin/Streptomycin and 5 x 10^{-5} M 2-mercaptoethanol. 2 x 10^5 spleen cells per well were incubated in 96 well microtitre plates with several concentrations of compound or with media only as the positive control. Triplicate cultures were run for each compound dose as well as for control wells. Compounds were prepared in dimethylsulfoxide (DMSO) at stock concentrations of 100 mg/mL and dilutions were prepared in CM. 5 μg/well of Con A (a T cell mitogen) was added to each well. Cultures were incubated for 24 hours at 37°C and 5% CO_2. Potential cytotoxic effects of the compounds were pre-determined by trypan blue exclusion viability testing of mouse cells exposed to varying concentrations of the specific compounds as described in Example 15. Only non-cytotoxic concentrations of compounds were tested. At the end of the incubation period, cellular proliferation was determined using a commercially available MTT kit (Promega G4000). The optical density (OD) of each well was read on a Molecular Devices microplate reader at 570-650 nm. Results are expressed as percent change from control which is determined using the following formula:

(OD unknown - OD control) / OD control x 100 = % change

Results: The potent inhibitory effects of compounds of formula I on mitogen induced T lymphocyte proliferation and activation are presented in Table 3. The potent inhibitory effects of compounds of formula II are shown in Tables 4A and 4B. A compound is considered active in the Con A stimulated T lymphocyte proliferation assay if a greater than -20% inhibition of the control proliferative response is achieved at a concentration within the 0.00001-10 μg/mL of compound dose range.

TABLE 3
Inhibition of Con A Stimulated*
T Lymphocyte Proliferation

Compound	*in vitro* concentration of compound (μg/mL)				
	10	1	0.1	0.01	0.001
Ib	-97	-23	-18	-20	-13
Ia	-99	-15	-15	-19	-12

* Results expressed as % change from control; nt = not tested

TABLE 4A
Inhibition of Con A Stimulated* T Lymphocyte Proliferation

Compound	*in vitro* concentration of compound (µg/mL)						
	10	1	0.1	0.01	0.001	0.0001	0.00001
IIaa	nt	-34	-23	-20	-17	nt	nt
IIg	0	-10	-14	-28	-34	-42	-48
IIgg	-95	-9	-15	-23	-20	nt	nt
IIh	-19	-19	-31	-21	-23	nt	nt
IIa	-91	-12	-28	-28	-27	nt	nt
IIii	-100	-17	-27	-26	-29	nt	nt
IIjj	-96	-211	-38	-55	34	-3	nt
IIkk	-96	-16	-17	-24	-13	nt	nt
IIll	-91	-22	-17	-20	-14	nt	nt
IIk	-62	-12	-15	-21	-11	nt	nt
IIl	-100	-12	-4	nt	nt	nt	nt
IIn	-32	-21	-20	-21	-21	nt	nt
IIq	-20	-29	-26	-18	-20	nt	nt
IIr	-99	-12	6	nt	nt	nt	nt
IIs	-60	-10	5	nt	nt	nt	nt
IIx	nt	-10	4	0	nt	nt	nt
IImm	-19	-27	-27	-21	-13	nt	nt
IInn	-18	-29	-36	-27	-12	nt	nt
IIb	-21	-22	-29	-20	-10	nt	nt

* Results expressed as % change from control; nt = not tested.

TABLE 4B
Inhibition of Con A Stimulated*
T Lymphocyte Proliferation

Compound	*in vitro* concentration of compound (μg/mL)						
	100	50	10	1	0.1	0.01	0.001
IIoo	nt	nt	-21	28	29	24	5
IIss	nt	nt	-30	23	14	9	9
IIvv	-86	5	40	42	35	38	13
IIww	nt	-99	24	26	29	25	8
IIxx	nt	nt	-31	13	19	1	-4
IIaaa	nt	nt	-92	14	11	17	6
IIddd	nt	-73	5	8	5	8	17
IIfff	nt	nt	-33	11	2	4	-3
IIlll	-97	-54	23	26	21	30	23
IInnn	nt	nt	-96	5	8	9	3
IIsss	nt	nt	nt	-24	-16	-22	-16

* Results expressed as % change from control; nt = not tested.

Example 17: *In vitro* Mixed Lymphocyte Response (MLR) Assay.

The potential immunomodulatory effects of compounds of the invention were studied in an *in vitro* MLR assay system. This assay tests the ability of a specific compound to regulate a cell mediated immune response involving T lymphocyte activation and proliferation.

Specific Method: Balb/cByJ (responder) and C57B1/6 (stimulator) mice were euthanized by cervical dislocation and their spleens were removed aseptically. Single cell splenic lymphocyte suspensions were prepared as described in Example 16. The C57Bl/6 cells were used as the stimulator cell type and were treated with mitomycin c to prevent proliferative activity. The proliferative response of responder cells to stimulator cells was measured by incubating 5 x 10^5 of each cell type per well together along with media alone (control) or with varying non-toxic concentrations of compound in 96 well microtitre plates. Compound cytotoxicity was monitored as described in Example 15. Triplicate cultures were run for each compound dose and for control wells.

Compounds were prepared as described in Example 16 and were added to the appropriate test wells. After 5 days incubation at 37°C and 5% CO_2, each well was pulsed overnight with 2μCi of ^{3}H-thymidine and harvested the next day on a PHD cell harvester. Cellular incorporation of ^{3}H-thymidine (cpm) was determined with a Packard scintillation counter. Results are expressed as percent change from control MLR's and are calculated using the following formula:

$$\frac{(\text{cpm unknown MLR} - \text{cpm control MLR})}{\text{cpm control MLR}} \times 100 = \% \text{ change}$$

Results: The potent inhibitory effects of compounds of formula I on in vitro mixed lymphocyte responsiveness are presented in Table 5. The potent inhibitory effects of compounds of formula II are presented in Table 6. A compound is considered active in the in vitro Mixed Lymphocyte Response Inhibition assay when greater than -30% inhibition of the control response is mediated at the 0.0001 - 10 μg/mL concentration range of compound.

TABLE 5

Mixed Lymphocyte Response Inhibition*

Compound	*in vitro* concentration of compound (µg/mL)					
	10	1	0.1	0.01	0.001	0.0001
Ib	-100	-52	-60	-39	-1	-16
Ia	-195	-112	-140	-47	-58	nt

* Results expressed as % change from control; nt = not tested

TABLE 6
Mixed Lymphocyte Response Inhibition*

Compound	*in vitro* concentration of compound (µg/mL)					
	10	1	0.1	0.01	0.001	0.0001
IIe	nt	-63	-53	-42	-52	-55
IIz	-7	-27	-50	-51	-5	-78
IIbb	-100	-62	-85	-51	-19	-21
IIc	-100	-34	0.5	-35	-21	43
IIf	-88	-14	-66	-8.7	-59	-14
IIg	-76	-92	-83	-60	-64	34
IIgg	-100	-100	-90	-83	-86	-30
IIhh	-55	-84	-75	-41	-45	21
IIh	-100	-63	-51	-91	-6	22
IIa	-100	-67	-83	-63	44	27
IIii	-100	-52	-49	-58	-0.1	37
IIjj	-96	-21	-38	-55	34	-3
IIkk	-100	-100	-38	-67	-2	-1
IIll	-100	-71	2	-10	28	0.3
IIp	nt	-36	-35	50	94	nt
IIs	-100	-70	-15	-8	-7	46
IIu	-100	-65	93	23	74	nt
IIx	nt	-28	-40	53	49	22
IIrrr	nt	-45	-43	-60	-31	nt
IIqqq	nt	-77	-65	-64	-43	nt
IIooo	-58	-72	-49	-65	-43	nt
IIppp	nt	-28	-33	-83	-71	nt
IIsss	nt	-34	122	-25	100	nt

* Results expressed as % change from control; nt = not tested

Example 18: *In Vitro* Mixed Lymphocyte Response (MLR) Assay Alternate Specific Method Used for Formula II Compounds

Specific Method: C5B1/6 (responder) and Balb/cByJ (stimulator) mice were euthanized by cervical dislocation and their spleens were removed aseptically. Single cell splenic lymphocyte suspensions were prepared as described in Example 14.

The Balb/cByJ cells were used as the stimulator cell type and were treated with mitomycin c to prevent proliferative activity. The proliferative response of the responder cells to stimulator cells was measured by incubating 4 x 10^5 of each cell type per well together along with media alone [control] or with varying non-toxic concentrations of compound in 96 well mitrotitre plates.

The remainder of the assay and data analyses were performed as described in Example 17. The results are shown in Table 7.

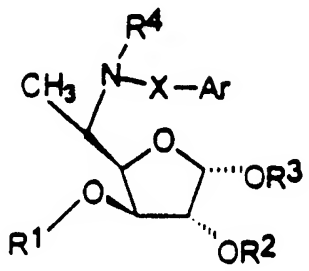
TABLE 7
Mixed Lymphocyte Response Inhibition*
in vitro concentration of compound (μg/mL)

Compound	100	50	10	1	0.1	0.01	0.001
IIoo	nt	nt	-84	-2	35	36	18
IIpp	nt	nt	nt	41	11	-29	-13
IIqq	nt	nt	-89	-5	-4	-12	7
IIrr	nt	nt	-103	-16	-24	-2	-4
IIss	nt	nt	-94	-21	4	-21	-4
IItt	nt	nt	-42	-34	15	22	5
IIuu	nt	nt	nt	-7	-30	-23	-4
IIvv	nt	nt	-1	-7	2	-22	-34
IIww	nt	-103	255	-6	7	-3	-33
IIxx	nt	nt	-96	15	5	13	-25
IIyy	nt	-67	-24	5	-4	13	16
IIzz	nt	nt	-88	-21	-30	-31	-19
IIaaa	nt	nt	-104	-10	-43	-22	-30
IIbbb	nt	-38	-102	-33	-44	-37	-28
IIccc	nt	nt	-98	-27	-32	-5	-26
IIddd	nt	-104	-88	-5	-32	-34	-27
IIeee	nt	nt	-99	-18	-41	-21	-25
IIfff	nt	nt	-104	-46	-52	-44	-32
IIggg	nt	-104	-42	-53	-34	-23	-35
IIhhh	nt	nt	nt	-27	-26	-27	-45
IIiii	nt	nt	-66	-32	-4	-25	-35
IIjjj	nt	nt	-90	-21	-36	-27	-24
IIkkk	nt	nt	28	2	6	-3	-33
IIlll	-104	-104	-40	-28	-34	-36	-12
IImmm	nt	nt	-96	-22	-31	-34	-34
IInnn	nt	nt	nt	-10	-35	-42	-33

*Results expressed as % change from control; nt - not tested

The claimed invention is:

1. A 5,6-dideoxy, 5-amino derivative of idose of the formula (I):



(I)

wherein

R^1 is a C_3 to C_{15} branched or unbranched alkyl group, or an alkyl-cycloalkyl group;

R^2 and R^3 together with the atoms carrying them form an acetal protecting group;

Ar is a substituted or unsubstituted, aromatic or heteroaromatic group selected from the group consisting of imidazolyl, furanyl, pyrrolyl, 1,3-benzodioxol-5-ylmethyl, pyridinyl, thienyl, naphthyl, and phenyl;

R^4 is hydrogen or a branched or unbranched lower alkyl group having 1 to 5 carbon atoms; and

X is a bond or a branched or unbranched lower alkylene group having 1 to 5 carbon atoms, or together with R^4, and the nitrogen carrying them, forms a 5-, 6-, or 7-membered heterocycle fused to said aromatic or heteroaromatic group Ar;

or a physiologically acceptable salt thereof.

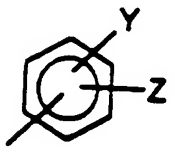
2. A 5,6-dideoxy, 5-amino derivative of idose of claim 1, wherein

R^1 is a C_4 to C_{12} unbranched alkyl group or a (C_1-C_3)-alkyl-(C_3-C_7)-cycloalkyl group;

R^2 and R^3 together with the atoms carrying them form an acetal protecting group selected from the group consisting of an isopropylidene and a cyclohexylidene group;

Ar is a substituted or unsubstituted, aromatic or heteroaromatic group selected from th group

consisting of furanyl, thienyl, pyridinyl, naphthyl and a phenyl group of the formula:



wherein

Y and Z are each independently H, F, Cl, Br, OCH_3, CN, NO_2, CF_3, OCF_3 or NR'R'', wherein R' and R'', which may be the same or different, are a branched or non-branched, substituted or non-substituted alkyl group;

R' is hydrogen, or a methyl, ethyl or propyl group; and

X is a bond or a branched or unbranched alkylene group having 1 to 5 carbon atoms, or together with R', and the nitrogen carrying them, form a hydrogenated isoquinoline group;

or a physiologically acceptable salt thereof.

3. The 5,6-dideoxy, 5-amino derivative of idose of claim 2, 1,2-O-isopropylidene-3-O-decyl-5,6-dideoxy-5-N-[(2-pyridinylmethyl)amino]-β,L-idofuranose, or a physiologically acceptable salt thereof.

4. The 5,6-dideoxy, 5-amino derivative of idose of claim 2, 1,2-O-isopropylidene-3-O-decyl-5,6-dideoxy-5-N-[(2-furanylmethyl)amino]-β,L-idofuranose, or a physiologically acceptable salt thereof.

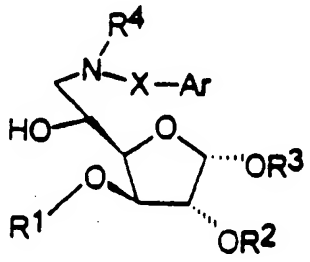
5. The 5,6-dideoxy, 5-amino derivative of idose of claim 2, 1,2-O-isopropylidene-3-O-decyl-5,6-dideoxy-5-N-[[2-(2-pyridinyl)ethyl]amino]-β,L-idofuranose, or a physiologically acceptable salt thereof.

6. A pharmaceutical composition for the treatment of an inflammatory and/or autoimmune disorder comprising an effective amount of a compound according to claim 1, or a physiologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

7. A method of treating an animal or human suffering from an inflammatory and/or autoimmune disorder comprising administering thereto the compound according to claim 1, or physiologically acceptable salt thereof, in an amount effective to treat an inflammatory and/or autoimmune disorder.

8. A method of claim 7, wherein the inflammatory and/or autoimmune disorder treated is rheumatoid arthritis, psoriasis, psoriatic arthritis, scleroderma, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, osteoarthritis, or asthma.

9. A 6-deoxy, 6-amino derivative of glucose of the formula (II):



(II)

wherein

R^1 is a C_3 to C_{15} branched or unbranched alkyl group, or an alkyl-cycloalkyl group;

R^2 and R^3 together with the atoms carrying them form an acetal protecting group;

Ar is a substituted or unsubstituted, aromatic or heteroaromatic group selected from the group consisting of imidazolyl, furanyl, pyrrolyl, 1,3-benzodioxol-5-ylmethyl, pyridinyl, thienyl, naphthyl, and phenyl;

R^4 is hydrogen or a branched or unbranched lower alkyl group having 1 to 5 carbon atoms; and

X is a bond, or a branched or unbranched lower alkylene group having 1 to 5 carbon atoms, or together with R^4, and the nitrogen carrying them, forms a 5-, 6-, or 7-membered heterocycle fused to said aromatic or heteroaromatic group Ar;

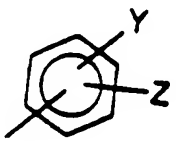
or a physiologically acceptable salt thereof.

10. A 6-deoxy, 6-amino derivative of glucose of claim 9, wherein

R^1 is a C_4 to C_{12} unbranched alkyl group or a (C_1-C_3)-alkyl-(C_3-C_7)-cycloalkyl group;

R^2 and R^3 together with the atoms carrying them form an acetal protecting group selected from the group consisting of an isopropylidene and a cyclohexylidene group;

Ar is a substituted or unsubstituted aryl group selected from the group consisting of furanyl, thienyl, pyridinyl, naphthyl and a phenyl group of the formula:



wherein

Y and Z are each independently H, F, Cl, Br, OCH_3, CN, NO_2, CF_3, OCF_3 or NR'R'', wherein R' and R'', which may be the same or different, are a branched or non-branched, substituted or non-substituted alkyl group;

R^4 is hydrogen, methyl, ethyl or propyl group; and

X is a bond, a branched or unbranched alkylene group having 1 to 5 carbon atoms, or together with R^4, and the nitrogen carrying them, form a hydrogenated isoquinoline group;

or a physiologically acceptable salt thereof.

11. A 6-deoxy, 6-amino derivative of glucose of claim 9, or a physiologically acceptable salt thereof, selected from

1,2-O-isopropylidene-3-O-decyl-6-deoxy-6-N-(1,2,3,4-tetrahydroisoquinolinyl)-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-decyl-6-deoxy-6-N-[[(3,4-difluorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(2-fluorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose hydrochloride,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(4-pyridinylmethyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(3-methoxyphenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[3-(N-imidazolyl)propyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[2-(2-pyridinyl)ethyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[(phenylmethyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[(3-pyridinylmethyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[4-(1-benzyl)piperidinyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[(2-trifluoromethylphenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[(4-trifluoromethylphenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[(3-trifluoromethylphenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[2-(3-chlorophenyl)ethyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[2-(4-chlorophenyl)ethyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-dodecyl-6-N-[[2-(2-chlorophenyl)ethyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-N-[[(2-methoxyphenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-N-[[(3-methoxyphenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-N-[[(4-methoxyphenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-dodecyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-dodecyl-6-deoxy-6-N-[(2-thienylmethyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(3-fluorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[2-(4-methoxyphenyl)ethyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(3-chlorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(4-chlorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(phenylmethyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[(3-phenylpropyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(1-methyl-3-phenyl)propyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[2-(1-methyl-1H-pyrrol-2-yl)ethyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-decyl-6-deoxy-6-N-[(1,3-benzodioxol-5-ylmethyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(2,4-dichlorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(2,3-dimethoxyphenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(3,5-dimethoxyphenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-decyl-6-deoxy-6-N-[[(3,4-dichlorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-decyl-6-deoxy-6-N-[[(2,6-difluorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-(3'-cyclohexylpropyl)-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-(3'-cyclohexylpropyl)-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(3-chlorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-(1,2,3,4-tetrahydroisoquinolinyl)-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(2-thienylmethyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(1-naphthylmethyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-pentyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-pentyl-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]-α,D-glucofuranose,

1,2-O-isopropylidene-3-O-pentyl-6-deoxy-6-N-[[(3-chlorophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclopropylmethyl-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclopropylmethyl-6-deoxy-6-N-[[(3-chlorophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-chlorophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-trifluoromethylphenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(3-fluorophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-pentyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclopropylmethyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-(3'-cyclohexylpropyl)-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(2,4-difluorophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-trifluoromethoxyphenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-(4-pyridinylamino)- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[(2-chlorophenyl)amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(3,4-difluorophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-bromophenyl)methyl]amino]- ,D-glucofuranose,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(4-pyridinylmethyl)amino]- ,D-glucofuranose hydrochloride,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(3-methoxyphenyl)methyl]amino]- ,D-glucofuranose hydrochloride,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]- ,D-glucofuranose hydrochloride,

1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(3-chlorophenyl)methyl]amino]- ,D-glucofuranose hydrochloride,

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]- ,D-glucofuranose hydrochloride, and

1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]- ,D-glucofuranose hydrochloride.

12. A compound of claim 9, wherein the compound is 1,2-O-isopropylidene-3-O-heptyl-6-deoxy- 6-N-[(2-pyridinylmethyl)amino]- ,D-glucofuranose hydrochloride.

13. A pharmaceutical composition for the treatment of an inflammatory and/or autoimmune disorder comprising an effective amount of a compound according to claim 9, or a physiologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

14. A method of treating an animal or human suffering from an inflammatory and/or autoimmune disorder comprising administering thereto the compound according to claim 9, or a physiologically acceptable salt thereof, in an amount effective to treat an inflammatory and/or autoimmune disorder.

15. A method of claim 14, wherein the inflammatory and/or autoimmune disorder treated is rheumatoid arthritis, psoriasis, psoriatic arthritis, scleroderma, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, osteoarthritis, or asthma.

16. A compound of claim 9, wherein the compound is 1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(3-methoxyphenyl)methyl]amino]- ,D-glucofuranose hydrochloride.

17. A compound of claim 9, wherein the compound is 1,2-O-isopropylidene-3-O-heptyl-6-deoxy-6-N-[[(2-chlorophenyl)methyl]amino]- ,D-glucofuranose hydrochloride.

18. A compound of claim 9, wherein the compound is 1,2-O-isopropylidene-3-O-h ptyl-6-deoxy-6-N-[[(3-chlorophenyl)methyl]amino]- ,D-glucofuranose hydrochloride.

19. A compound of claim 9, wherein the compound is 1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[[(4-fluorophenyl)methyl]amino]- ,D-glucofuranose hydrochloride.

20. A compound of claim 9, wherein, the compound is 1,2-O-isopropylidene-3-O-cyclohexylmethyl-6-deoxy-6-N-[(2-pyridinylmethyl)amino]- ,D-glucofuranose hydrochloride.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/06429

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/70; C07H 3/02, 15/02
US CL :514/25; 536/17.2, 17.9, 22
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/42; 536/17.2, 22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,273,766 (STANEK) 16 JUNE 1981, see columns 1-5.	1-6, 9-13, and 16 -20
Y	US, A, 4,192,868 (TRONCHET ET AL.) 11 MARCH 1980, see columns 1-6.	1-20
Y	US, A, 4,521,240 (LOH) 04 JUNE 1985, see column 1 line 53 to column 2 line 57.	1-5, 9-12, and 16-20
Y	US, A, 4,554,011 (LOH) 19 NOVEMBER 1985, see column 1 line 26 to column 2 line 16.	1-5, 9-12, and 16-20
Y	US, A, 4,497,649 (LOH) 05 FEBRUARY 1985, see column 1 line 64 to column 2 line 64.	1-5, 9-12, and 16-20
Y	US, A, 4,994,572 (FLEET) 19 FEBRUARY 1991, see column 3 line 44 to column 6 line 28.	1-6, 9-13, and 16-20

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
09 SEPTEMBER 1994

Date of mailing of the international search report
SEP 19 1994

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application N .
PCT/US94/06429

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,200,523 (FLEET) 06 APRIL 1993, see column 3 line 47 to column 6 line 26.	1-6, 9-13, and 16-20
Y, P	US, A, 5,248,779 (FLEET) 28 SEPTEMBER 1993, see column 4 line 6 to column 6 line 39.	1-6, 9-13, and 16-20
Y	US, A, 4,996,195 (RONSEN ET AL.) 26 FEBRUARY 1991, see column 2 lines 13-62.	1-20
Y	US, A, 5,010,058 (RONSEN ET AL.) 23 APRIL 1991, see column 2 line 16 to column 4 line 24.	1-20
Y	US, A, 4,738,953 (GORDON) 19 APRIL 1988, see column 2 line 31 to column 11 line 43.	1-20
Y	US, A, 4,735,934 (GORDON) 05 APRIL 1988, see column 1 line 63 to column 11 line 57.	1-20
Y	US, A, 4,056,322 (GORDON ET AL.) 01 NOVEMBER 1977, see column 2 line 40 to column 8 line 19.	1-6, 9-13, and 16-20
Y	CARBOHYDRATE RESEARCH, Volume 15, issued 1970, C. F. Gibbs et al. "5-Acetamido-5,6-dideoxy-L-Idose" pages 29-34, see pages 29-31.	1-6, 9-13, and 16-20
Y	JOURNAL OF THE CHEMICAL SOCIETY D, CHEMICAL COMMUNICATIONS, Vol. 20, issued 1969, C. F. Gibbs et al., "5-Amino-5,6-Dideoxy-L-Idose" page 1210, see the whole article.	1-6, 9-13, and 16-20
Y	MATERIALS RESEARCH SOCIETY SYMPOSIUM PROCEEDINGS, Vol. 174, issued 1990, M. R. Callstrom et al., "New Carbohydrate-Based Materials" pages 259-266, see page 261.	1-6, 9-13, and 16-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/06429

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

STN files searched: Registry, CA. Search terms: dideoxy, amino, idose, deoxy, amino, glucose?, isopropylidene, glucofuranose

APS file searched: USPAT. Search terms: 5,6-dideoxy, 6-deoxy, isopropylidene, glucofuranose